DRAFT
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Public Health Goal for
URANIUM
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

February 2000

LIST OF CONTRIBUTORS

PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR URANIUM IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.2 ppb (0.2 pCi/L) is proposed for natural uranium in drinking water based on a study showing changes in indicators of kidney function (β2-microglobulin and γ-glutamyl transferase levels in the urine) in a human population. This proposed PHG has been calculated from a NOEL of 3 μg/day with an uncertainty factor of 10 for intrahuman variability. This proposed PHG is also protective against carcinogenic effects of ionizing radiation produced by uranium. The theoretical cancer risk at the proposed PHG is estimated at 5×10^{-7}. OEHHA considers theoretical risks below 10^{-6} to be negligible. Uranium is a naturally occurring radioactive element that is ubiquitous in the earth's crust. Uranium is found in ground and surface waters due to its natural occurrence in geological formations. The average uranium concentrations in surface, ground and domestic water are 1, 3 and 2 pCi/L, respectively. The uranium intake from water is about equal to the total from other dietary components. Natural uranium contains 99.27 percent ^{238}U, 0.72 percent ^{235}U and 0.006 percent ^{234}U by weight. The primary noncarcinogenic toxic effect of uranium is on the kidneys. Recently published studies in rats, rabbits, and humans show effects of chronic uranium exposure at low levels in drinking water. Effects seen in rats, at the lowest average dose of 0.06 mg U/kg-day, including histopathological lesions of the kidney tubules, glomeruli and interstitium are considered clearly adverse effects albeit not severe. Histopathological effects were also seen at the same exposure level in the liver including nuclear anisokaryosis and vesiculation. Effects on chemical indicators of kidney function were seen in urine of humans exposed to low levels of uranium in drinking water for periods up to 33 years. These effects, such as increased urinary glucose, β2-microglobulin, and γ-glutamyl transferase, are indicative of potential kidney injury rather than toxicity per se. Uranium is an emitter of ionizing radiation, and ionizing radiation is carcinogenic, mutagenic and teratogenic. A level of 0.2 ppb (0.2 pCi/L) is considered protective for both kidney toxicity and carcinogenicity and is therefore proposed as the PHG for natural uranium in California drinking water.

The U.S. Environmental Protection Agency (U.S. EPA) has not established a Maximum Contaminant Level (MCL) for natural uranium, but does have an MCLG of 0. The State of California has an MCL for uranium of 20 pCi/L based on earlier studies of toxicity to the kidney. The rabbit study used in the risk assessment on which the California MCL is based (Novikov and Yudina, 1970) has been superseded by more recent studies of the effects of uranium on kidney function in laboratory animals and in human populations (Gilman et al., 1998a-c; Zamora et al., 1998; Health Canada, 1998).

INTRODUCTION

Uranium occurs as a trace element in many types of rocks. Because its abundance in geological formations varies from place to place, uranium is a highly variable source of contamination in drinking water. U.S. EPA has not established a Maximum Contaminant Level (MCL) for natural uranium, but has proposed a health guidance level of 10 pCi/L (Cothern and Lappenbusch,

1983). U.S. EPA reported in the Federal Register (Fed. Reg. 51: 34836, September 30, 1986) that the Maximum Contaminant Level Goal (MCLG) should be set at zero for natural uranium based on carcinogenicity of ionizing radiation.

Other agencies have developed health protective levels for uranium (see page 25). These differ from each other and provide equivocal guidance for setting a PHG for natural uranium. The purpose of this document is to review the evidence on toxicity of natural uranium and to derive an appropriate PHG for natural uranium in drinking water.

CHEMICAL PROFILE

Uranium is a radioactive metallic element (atomic number 92). Naturally occurring uranium contains 99.27 percent ^{238}U, 0.72 percent ^{235}U and 0.006 percent ^{234}U. One microgram (μg) of natural uranium has an activity of 0.67 pCi (Cothern and Lappenbusch, 1983). This is the equilibrium specific activity for natural uranium. Natural uranium in geological formations usually has this specific activity. Natural uranium in drinking water may not be in equilibrium, and therefore its specific activity may vary, as discussed below.

U.S. EPA proposed a definition of the term "natural uranium" as uranium with a varying composition, but typically with the composition given above (Fed. Reg. 51: 34836, September 30, 1986). On an equal weight basis the radioactivity of ^{234}U is 17,000-fold and that of ^{235}U is six-fold greater than that of ^{238}U (NRC, 1980). Uranium may be found in valence states of +2, +3, +4, +5 or +6, but +6 is the most stable form and exists as the oxygen-containing uranyl cation (UO_2^{+2}) (Cothern and Lappenbusch, 1983).

The best known use of uranium is as a source of fuel for nuclear reactors and nuclear bombs. The fissionable form of uranium is the isotope ^{235}U. This isotope is only a small fraction of naturally occurring uranium. Several complex minerals are of commercial importance, including carnotite, pitchblende and tobernite (Stokinger, 1981).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

U.S. EPA measured ambient air levels of uranium in 51 urban and rural areas of the United States (U.S.) (U.S. EPA, 1986). The measured concentrations ranged from 0.011 fCi/m^3 to 0.3 fCi/m^3. Ambient air is unlikely to be a significant source of exposure to uranium outside of mining and occupational settings.

Soil

Uranium is present in soils and rocks in concentrations generally varying between 0.5 and 5 ppm (NRC, 1983). It is found in granites, metamorphic rocks, lignite, monazite sands and phosphate deposits as well as in minerals (Cothern and Lappenbusch, 1983). Uranium enters other media (air, water and food) from the rocks and soil.

Water

The naturally occurring uranium concentration in drinking water sources depends on factors such as the uranium concentration in the host aquifer rock, the partial pressure of CO_2, the presence of O_2 and complexing agents in the aquifer, the pH and the nature of the contact between the uranium minerals and water (Hess et al., 1985). Uranium in water is derived from phosphate deposits and mine tailings, as well as from run-off of phosphate fertilizers from agricultural land. Greater than 99 percent of uranium transported by runoff from land to fresh water systems is in suspended particles and remains in the sediment (Cothern and Lappenbusch, 1983). Environmental pH also influences both the type and relative amount of chemical complexing agents present in solution, which are known to facilitate uranium solubility and mobility.

The average amount of uranium in drinking water in the U.S. is 2 pCi/L. Of 59,812 community drinking water supplies in the U.S., 25 to 650 exceeded a uranium concentration of 20 pCi/L; 100 to 2,000 exceeded 10 pCi/L; and 2,500 to 5,000 exceeded 5 pCi/L (Cothern and Lappenbusch, 1983).

Some water supplies contain more activity from ^{234}U than from ^{238}U, resulting in a $^{234}U/^{238}U$ activity ratio greater than one. It has been observed that the largest disequilibrium ratio occurs in slightly oxidizing environments. The activity ratio is seldom less than one and rarely exceeds two (Cothern and Lappenbusch, 1983). The radioactivity calculated for ^{234}U and ^{238}U, determined by chemical uranium analysis, and using the equilibrium factor of 0.67 pCi/µg, will be in error if the two isotopes are not in equilibrium. The actual factor can range from 0.33 pCi/µg (no ^{234}U) to at least 7 pCi/µg ($^{234}U/^{238}U = 20$) (Blanchard et al., 1985). U.S. EPA has estimated a specific activity of 1.3 pCi/µg for uranium in drinking water sources based on the results of a nationwide survey (Fed. Reg. 56: 33050-33127, July 18, 1991). The relative abundance of isotopes in a drinking water source depends on physical and chemical factors (such as an oxidizing environment, and the rate of removal of uranium compounds from rocks or soil) and varies greatly from place to place (Cothern and Lappenbusch, 1983). For this reason U.S. EPA's estimate does not necessarily apply to California drinking water sources. Fluorimetric methods for uranium determination have the necessary sensitivity and accuracy for estimating water concentrations to 10 pCi/L (Blanchard, et al., 1985).

In 1984 California Department of Health Services (CDHS) conducted an extensive investigation of radioactivity in ground water in the community of Glen Avon. Four samples had levels greater than 40 pCi/L. Forty-eight samples had uranium activity between 10 and 40 pCi/L. Eight samples had less than 10 pCi/L. Apparently acidic ground water is responsible for mobilizing naturally occurring uranium in the soil (CDHS, 1985).

Wong, et al. (1999) studied the isotopic abundance ratios of natural uranium in selected California groundwater. Representative samples from 102 groundwater locations throughout the state were analysed for gross alpha by internal proportional counting, total uranium by laser phosphorimetry and total uranium by inductively coupled plasma-mass spectrometry (ICPMS). Selected samples (43) were analysed for isotopic abundances of ^{234}U, ^{235}U, and ^{238}U. The average $^{234}U/^{238}U$ activity ratio for the study was 1.32 ± 0.30 SD. The average activity to mass conversion factor (specific activity) was 0.79 pCi/µg with a standard deviation of 0.10. The latter data set from Wong et al. (1999) was analyzed using Microsoft Excel (Version 4) Crystal Ball (Version 4, Decisioneering, Inc) and the normal distribution was found to best fit the data.

Food

Because uranium is present in many soils and in some water supplies, it also occurs in many foods. The use of phosphate fertilizers increases the uranium level in foods. The National Council on Radiation Protection and Measurements (NCRPM) has estimated that humans take in approximately the same amount of uranium in food as they do in drinking water (NCRPM, 1984). This would suggest a relative source contribution (RSC) in the range of 40 to 60 percent for use in calculating a PHG based on experiments in which total uranium exposure is measured.

METABOLISM AND PHARMACOKINETICS

Absorption

Inhalation is a minor route of entry for uranium into humans in the general population. The use of water that contains uranium could expose an individual to uranium by dermal contact or ingestion. Human skin absorption data are not available. Percutaneous absorption has been reported as an effective route of penetration for soluble uranium compounds after application to rat skin (De Rey et al., 1983). Single or daily applications were performed with uranium compounds mixed with emulsion composed of Vaseline® and water (De Rey et al., 1983). The lowest administered dose (0.5 g/kg body weight) was orders of magnitude greater than could result from exposure to the highest levels of uranium found in potential California drinking water sources. Electron microscopy showed that the uranium penetrated into the intercellular space between the horny and granular layers of the epidermis. Adverse effects such as purulence and detachment of the horny layer were observed (De Rey et al., 1983).

Gastrointestinal absorption studies of uranium include single oral administration experiments of soluble uranium compounds to rats, dogs, hamsters, baboons and neonatal swine. Gastrointestinal absorption is consistently lower in rats (less than 0.5 percent) than in other species studied (Wrenn et al., 1985). Fractional absorption in 2 day old rats given uranyl nitrate orally was estimated as 0.01 to 0.07 (ICRP, 1995). In feeding studies it was found that absorption was doubled in fasted rats, and increased 3.4 fold in iron-deficient rats (ATSDR, 1997).

Average absorption was reported to be 1.55 percent (0.83 to 2.3 percent) for seven dogs (Fish et al., 1960). Gastrointestinal absorption for adult Syrian hamsters was calculated to be 0.77 percent (Harrison and Stather, 1981). $UO_2(NO_3)_2$ given by gavage to one-day old miniature swine at a dose of 1.5 to 2.0 mg uranium/kg showed absorption of at least 34.5 percent (Sullivan and Gorham, 1982).

There is limited published information on gastrointestinal absorption of uranium in humans. Hursch et al. (1969) studied oral uranium absorption in four male hospital patients (ages 56 to 78 years). $UO_2(NO_3)_2$ (10.8 mg) dissolved in 100 mL Coca Cola® was ingested by each subject after an overnight fast. Urine and fecal samples were collected and analyzed for uranium. The four subjects showed uranium absorption of 0.3, 0.7, 1.1, and 3.3 percent. Unabsorbed uranium passes into the feces. Daily excretion of uranium in urine approximates the uranium absorbed from food and drink. Hursch and Spoor (1973) cited data indicating that between 12 and

30 percent of uranium ingested in the normal diet is absorbed from the gastrointestinal tract. The levels of natural uranium in food and water are lower than those used experimentally.

In general, the smaller the amount of uranium ingested, the greater the fraction absorbed (Wrenn et al., 1985). On the basis of a U.S. survey (Welford and Baird, 1967) it was estimated that the intake of uranium from the normal diet is 1.75 μg/day, and that the extent of gastrointestinal absorption was 7.7 percent (Wrenn et al., 1985). Fisher et al. (1983) reported that uranium absorption for three controls was 0.6 to 1 percent and for three retired uranium workers it was 0.55 to 1.6 percent. Somayajulu et al. (1980) collected urine and feces in summer and winter from one individual. The estimated uranium absorption for the summer sample was 3.8 percent and for the winter sample was 0.57 percent. Wrenn et al. (1985) using data from three human studies and six animal experiments, gave a best estimate of gastrointestinal absorption of uranium for adult humans at environmental levels of uranium intake of 1.4 percent. From all the data sets available Wrenn et al. found a range of mean values of 0.3-7.8 percent of ingested uranium absorbed, with a grand mean of 1.8 percent. No values for human neonates were given. Gastrointestinal absorption of ^{238}Pu (plutonium) was about 100 times higher in neonatal rodents than in adult rodents and this difference was 10 to 20 times greater in swine (Sullivan, 1980). Absorption of uranium by neonatal swine is higher than absorption of Pu from the gastrointestinal tract (Sullivan and Gorham, 1982).

Enhanced permeability of the intestine of the neonate facilitates passage from the nursing mother's milk to the neonate of macromolecules that are essential to immunity (Sullivan and Gorham, 1982). Uranium may be associated with proteins during passage across the intestinal mucosa. Absorption of iron and other heavy metals increases during lactation (Batey and Galagher, 1977; Bhattacharrya et al., 1981 and 1982; Kostial and Momcilovic, 1972). Certain dietary constituents can enhance the absorption of lead (Blake, 1983) and cadmium (Smith and Foulkes, 1985). Therefore it is reasonable to assume that sensitive members of a population may have higher gastrointestinal absorption of uranium than healthy adults.

In its review of the literature, U.S. EPA found values for gastrointestinal absorption of uranium in humans ranging from 1 to 30 percent (U.S. EPA, 1991a, b). For purposes of calculating the cancer risk of natural uranium in drinking water, U.S. EPA chose 20 percent as the "best estimate" acknowledging that there is "substantial uncertainty" associated with this number (U.S. EPA, 1991a, b).

The latest guidance from U.S. EPA on gastrointestinal absorption of uranium is found in Federal Guidance 13 (U.S. EPA, 1999). This document gives gastrointestinal absorption fractions (f1 values) for uranium of 2 percent for children aged 1 to 15 years, and 2 percent for adults. The value listed for infants is 4 percent. U.S. EPA took these data from the International Commission on Radiological Protection (ICRP, 1995).

Distribution and Excretion

Bicarbonate complexes are the chief form in which uranium is absorbed and transported within the human body (Hodge, 1973). $UO_2(HCO_3)_2$ in plasma is taken up by bone and filtered by the glomeruli into the urine (Durbin and Wrenn, 1975). Most of the studies involving distribution and excretion of uranium have been based on administration by intravenous or intraperitoneal injection, feeding or inhalation to animals. Stevens et al. (1980) measured the distribution, retention and excretion of ^{233}U in seven beagles injected intravenously with 2.8 μCi ^{233}U per kg

body weight, and sacrificed at times ranging from 1 to 726 days post injection. Twenty-two percent of the injected uranium was found in the kidney at one day post injection with high concentrations localized in the proximal tubules and 7.7 percent of the uranium was found in the skeleton. In a study with female mice exposed orally to uranyl nitrate hexahydrate at a dose of 462 mg/kg-day for 36 to 44 weeks, average uranium accumulation was 6 μg per pair of kidneys, 46 μg/mg bone, and 0 to 0.5 μg/mg whole liver (Tannenbaum et al., 1951). Autoradiographic studies in Sprague-Dawley rats showed that, in bone, uranium accumulates mainly in the cancellous portion (trabeculae) and endosteum; whereas accumulation in the kidney occurs in the cortex and in the corticomedullary junction (Tannenbaum et al., 1951).

The kidneys and bones are the principal sites of accumulation and toxic action of uranium (Yuile, 1973; Stevens et al., 1980; Morrow et al., 1982). Following uranium administration, 80 percent is excreted in urine and feces, 10 percent is deposited in the kidneys and the remaining 10 percent is deposited in the skeleton with negligible concentrations appearing in other tissues (NRC, 1983). The skeleton is the major site of long-term storage of uranium (Wrenn and Singh, 1982).

Several studies have reported the amount of uranium in the skeleton of persons with no known occupational exposure to uranium. The average values ranged from 2.3 to 61.6 μg with a mean value of 24.9 ± 22 μg uranium in 5,000 grams of bone (Wrenn et al., 1985).

Kathren et al. (1989) reported uranium concentrations in tissues collected at autopsy from an occupationally exposed individual. Deposition of uranium followed the pattern: skeleton > liver > kidney, with ratios of 63:2.8:1. The rank order of uranium content was in agreement with the observations by Fisenne and Welford (1986) for New York City residents but in disagreement with the data reported for the ICRP Reference Man (ICRP, 1975). The uranium order content in the Reference Man is skeleton > kidney > lung > liver or 59, 7, 1, 0.45 μg, respectively. Recently, uranium in all tissues of two whole bodies were measured and reported by the U.S. Transuranium and Uranium Registries (USTUR) (Kathrin, 1998). The data showed lung > kidney > liver in one case and kidney > lung > liver in the other. In both cases pulmonary lymph nodes were an order of magnitude higher in uranium concentration than other soft tissues. Such differences may be due to sampling error or real differences in exposure history and individual variability.

In humans, most of the uranium (approximately 90 percent) is excreted in the feces; the remainder is excreted in the urine (Wrenn et al., 1985). In rats, most of the absorbed dose leaves the body within a few days in the urine (ATSDR, 1997); half is excreted in two to six days (Durbin and Wrenn, 1975), and 98 percent is excreted within seven days (Sullivan et al., 1986).

There is a fast and a slow phase of uranium excretion in humans and animals. The retention half lives of uranium in bone and kidney are of most relevance. For bone, half-lives of 883 days (Stevens et al., 1980), 180 and 360 days (Hursh and Spoor, 1973) and 800 days (Bernard, 1958) have been reported. Retention half-lives for uranium in human kidney have been reported as 30 days (Bernard, 1958) and more recently as 6 days and 1,500 days for the fast and slow components, respectively (ICRP, 1979). Wrenn et al. (1985) utilized a 15-day half-life (Hursh and Spoor, 1973) and this value was incorporated into the uranium pharmacokinetic model.

Biokinetic Models

Biokinetic models mathematically characterize the movement, translocation, fate, deposition and excretion of a substance (e.g., uranium) in a living system. Such models predict where substances go in the body, and how long they remain, which permits the calculation of internal doses and risks to specific tissues and organs as well as the whole body (Kathrin, 1998). Such models may be generally descriptive of the retention of radionuclides in the body with virtual compartments or physiological where model compartments represent actual body organs and tissues. In the dose-computation scheme of the ICRP, information on the biological behavior of radionuclides is contained in three main types of biokinetic model: a respiratory model, a gastrointestinal (GI) model, and an element-specific systemic model.

The gastrointestinal model is used to describe the movement of swallowed or endogenously secreted material through the stomach and intestines. Element-specific gastrointestinal absorption fractions (F1 values) describe the rate and extent of absorption from the small intestine to blood (U.S. EPA, 1999). The GI model developed by U.S. EPA (1999) has been used by ICRP for many years. The model divides the GI tract into four compartments: stomach (St); small intestine (SI); upper large intestine (ULI); and lower large intestine (LLI), and assumes first-order transfer of material from one compartment to the next. Absorption of ingested material to blood is assumed to occur only in SI in terms of a fraction F1. The fraction (F1) of ingested material moves from SI to BLOOD and the fraction 1-F1 moves from SI to ULI and eventually via excretion to FECES. The transfer coefficient from SI to BLOOD is

$6F1/(1\text{-}F1)\ d^{-1}$.

The source of the uranium systemic biokinetic model used by U.S. EPA (1999) is ICRP (1995). The ICRP's physiologically based models for bone-seeking elements were developed within two frameworks: one designed for the class of "calcium-like" or bone volume filling elements such as strontium, radium and lead; and the other designed for the class of "plutonium-like" or bone-surface-seeking radionuclides such as thorium. The uranium model is of the calcium-like type. The model incorporates a central blood Plasma and RBC compartment connected to tissue compartments: Skeleton, Kidneys, Liver, and Other Soft Tissues, and to output compartments: GI Tract and Feces, Urinary Bladder and Urine. The tissue compartments are subdivided into sub-compartments of faster or slower turnover. The implementation of the model is described by Leggett et al. (1993). A simpler five compartment exponential model has been proposed by Fisher et al. (1991) based on an acute accidental occupational inhalation exposure of 31 workers to UF_6. In this model the fractional urinary excretion Y(t) is predicted as a function of time (in days) after exposure. The excretion constants of the five exponential compartments correspond to residence half-times of 0.25, 6, 26, 300, and 3,700 days in the lungs, kidneys, other soft tissues, and two bone compartments, respectively.

TOXICOLOGY

Toxicological Effects in Animals

Numerous animal studies of the toxicity of uranium have been undertaken, beginning with the Manhattan Project in the 1940s. These studies have been reviewed by Yuile (1973). More recently, the toxicology of uranium in animals has been reviewed by Durbin and Wrenn (1975) and by Wrenn et al. (1985).

Acute Toxicity

The acute oral toxicity of uranium compounds is low. There are large differences in sensitivity to uranium among the species tested. The LD_{50}s of intraperitoneal uranium nitrate ranged from 0.1 to 0.3 mg/kg in the rabbit and guinea pig to as much as 20 to 25 mg/kg in mice (Durbin and Wrenn, 1975). The approximate lethal doses of $UO_2(NO_3)_2$ administered intravenously to four species are given in Table 1.

Table 1. Lethal Doses (LD_{50}) of Uranium Administered Intravenously

Species	Lethal Dose (mg uranium/kg)	Dose Ratio
rabbit	0.1	1
guinea pig	0.3	3
rat	1.0	10
mouse	10 to 20	100 to 200

Nine days after a single intravenous injection of 2.8 μCi ^{233}U/kg or 2.8 μCi natural uranium/kg, a marked elevation of the blood urea nitrogen (BUN) was observed in all dogs tested (Stevens et al., 1980). Two episodes of azotemia (retention in the blood of excessive amounts of nitrogenous compounds) were noted. The first increase in BUN was attributed to chemical toxicity rather than radiation-induced toxicity because a similar effect was observed in the dogs given natural uranium instead of ^{233}U. Nine weeks after injection, a secondary episode of azotemia occurred in the dogs injected with ^{233}U, but not in the dogs injected with natural uranium. The authors hypothesized that the secondary increase may have been radiation-induced. Stevens et al. (1980) commented that following prolonged exposure of beagle dogs to ^{232}U or ^{233}U, the skeleton and not the kidney may be the primary target organ and osteosarcoma may be the cause of death.

Subchronic and Chronic Toxicity

Noncarcinogenic Effects

In a study of 30 dogs administered $UO_2(NO_3)_2$ (Yuile, 1973) in the diet for one year at dose levels of 0.0002 to 10 g/kg, adverse effects on growth were noted only for those dogs receiving 0.2 g/kg of uranyl nitrate.

Morrow et al. (1982) published inhalation studies with uranium on dogs. They found that an absorbed dose of approximately 10 μg/kg body weight produced renal injury and proposed that a concentration of 0.3 μg/g kidney is the threshold concentration for renal injury in dogs. The mechanism of toxic action on the kidney postulated by Hodge (1973) and Nechaey et al. (1981) was that UO_2^{++} may compete with Mg^{++} and Ca^{++} at ATP binding sites for these metals, thus disrupting active transport across the cell membrane.

Studies conducted from one day to five years showed that dogs, monkeys and rats could breathe a $UO_2(NO_3)_2$ aerosol at 5.8 mg/m^3 of air with little evidence of serious injury (Leach et al., 1970). Following the five-year exposures, groups of animals were held for postexposure study as long as 6.5 years (Leach et al., 1973). Pulmonary neoplasia developed in a high percentage of the dogs examined two to six years after exposure. Pulmonary and tracheobronchial lymph node fibrosis was more marked in monkeys than in dogs.

Novikov (1970) pointed out that acute and chronic uranium poisoning produces disturbances, not only in the kidney, but also in the cardiovascular system, the blood and hematopoietic system, the immune system, the thyroid, adrenal gland and liver, and in basal metabolism. Novikov (1970) stated that the use of the uranium concentration in the kidney as the sole criterion of toxicity is untenable because of toxicity in other organ systems. Novikov and Yudina (1970) examined the effects of 0.02, 0.2 and 1.0 mg/kg of uranium administered orally for 12 months to rabbits. They observed no changes in serum urea, creatinine and chloride levels. A dose of 1.0 mg/kg inhibited nucleic acid metabolism in rabbit kidney and liver.

Braunlich and Fleck studied the nephrotoxicity of uranyl nitrate in rats of different ages (1981). They found that alkaline phosphatase in the urine was a good indicator of nephrotoxicity for all rats except the very young and old (Braunlich and Fleck, 1981).

Gilman et al. (1998a) studied the toxic effects of uranium administered to rats in drinking water. Following a 28-day range finding study, five groups of 15 male and 15 female weanling Sprague-Dawley rats were exposed for 91 days to uranyl nitrate hexahyrdate (UN) in drinking water at 0.96, 4.8, 24, 120, or 600 mg UN/L. A control group was given tap water with less than 0.001 mg U/L. No dose-related effects on hematological or biochemical parameters were seen. Histopathological lesions were observed in the kidney and liver, in both males and females, in all dose groups. Renal lesions of tubules (apical nuclear displacement and vesiculation, cytoplasmic vacuolation, and dilation), glomeruli (capsular sclerosis), and interstitium (reticulin sclerosis and lymphoid cuffing) were observed in the lowest exposure groups. However, these do not generally increase in the higher dose groups. The authors identified a study LOAEL of 0.96 mg UN/L drinking water, equivalent to average doses of 0.06 and 0.09 mg U/kg-d in male and female rats, respectively.

Gilman et al. (1998b) exposed male New Zealand White (NZW) rabbits for 91-days to 0.96, 4.8, 24, 120, or 600 mg UN/L in drinking water. Subsequently females were similarly exposed for 91-days to 4.8, 24, or 600 mg UN/L. No dose-related changes in hematological or biochemical parameters were observed. Dose dependent effects were seen primarily in the kidney, where changes in the renal tubules were characteristic of uranium toxicity. The authors identified a study LOAEL of 0.96 mg UN/L in drinking water, equivalent to an average dose in males of 0.05 mg U/kg-d. The reversibility of uranium kidney toxicity was also investigated by Gilman et al. (1998c). Specific-pathogen free (SPF) male NZW rabbits were exposed to 24 or 600 mg UN/L in drinking water for 91 days. Recovery periods were 0, 8, 14, 45, or 91 days. Renal tubular injury with degenerative nuclear changes, cytoplasmic vacuolation, and tubular dilation was seen in the high dose group, without consistent resolution even after 91 days recovery.

Reproductive and developmental effects have been studied in rodents by several groups of investigators. These studies are summarized in U.S. EPA's drinking water criteria document (U.S. EPA, 1991b). In general, uranium salts cause reproductive and developmental effects (e.g., embryolethality, malformations and testicular effects) only when administered at much higher doses than those that would cause nephrotoxicity.

Carcinogenic Effects

Sarcomas resulted in rats injected with metallic uranium in the femoral marrow and in the chest wall (Hueper et al., 1952). The authors were unable to determine whether the local tumors induced by uranium were caused by metallocarcinogenic or radiocarcinogenic action. Alpha-emitting, bone-seeking radionuclides such as ^{232}U, ^{233}U and ^{226}Rn have been shown to induce bone tumors in rodents (U.S. EPA, 1991a, b). In general ionizing radiation is regarded by U.S. EPA as carcinogenic, mutagenic and teratogenic in animals and humans (U.S. EPA, 1991a, b).

Toxicological Effects in Humans

Acute Toxicity

One case study reported two deaths of human beings accidentally exposed to uranium hexafluoride and its breakdown products (uranyl fluoride and hydrofluoric acid) by inhalation (ATSDR, 1997). The acute effects of this exposure were characteristic of hydrofluoric acid exposure. No studies were found of acute effects to humans resulting from oral exposure to uranium or uranium compounds. Levels of $UO_2(NO_3)_2$ below 70 μg/kg administered intravenously to six terminally ill patients (Hursh and Spoor, 1973) did not produce renal injury as evidenced by changes in urinary proteins and catalase.

Chronic Toxicity

Noncarcinogenic Effects

The human data on uranium toxicity have been summarized by Hursh and Spoor (1973), Adams and Spoor (1973) and by Boback (1975). Boback (1975) found no abnormal clinical chemistry

parameter effects in urine from uranium workers involved in exposure incidents which produced urinary uranium concentrations up to 2.85 mg/L. Clarkson and Kench (1952) found low but significantly elevated levels of amino acids in the urine of 12 workers exposed to uranium hexafluoride.

Short-term follow-up studies in the 1940s and 50s of uranium workers exposed for several months or years to high levels of soluble uranium compounds showed only transient kidney damage (proteinuria) and no evidence of permanent effects (Hursh and Spoor, 1973).

Moss and McCurdy (1982) reported that increased β2-microglobulin (BMG) excretion in urine could be correlated with uranium in drinking water at concentrations up to 0.7 mg/L. Under normal conditions, only small amounts of protein are detected in the urine (Zamora, et al., 1998). Excretion of low molecular weight proteins such as BMG may increase as a result of increased plasma concentration or decreased tubular absorption (Zamora, et al., 1998). Even among those individuals who drank water with the highest uranium concentration, there were no overt signs of kidney dysfunction, nor histories of kidney ailments. No subtle changes in kidney function were revealed by clinical chemistry. Wrenn and Singh (1981) concluded that the skeleton is the major site of storage of uranium, but the kidney is the principal site of uranium injury after it once gains entrance to the circulation. More recently, Thun et al. (1985) found significantly higher urinary excretion of β2-microglobulin and five amino acids in uranium workers than in a reference group. Increased renal excretion was associated with length of exposure to soluble uranium. These data were consistent with uranium-induced nephrotoxicity.

Uranium has a pronounced tissue toxicity quite apart from its potential toxicity to the skeleton. Chen et al. (1961) concluded that ^{238}U would not pose a radiological hazard in humans because the quantities necessary to deposit sufficient uranium in bone to cause radiation effects would be far in excess of the uranium doses causing lethal renal damage. More recent analyses of the potential carcinogenic effects of natural uranium due to ionizing radiation do not agree with this conclusion (U.S. EPA, 1991a, b).

Zamora et al. (1998) studied the effects of uranium exposure in 50 subjects in two Canadian communities. The first had private wells supplied from a groundwater source whose uranium content was well above the current Canadian drinking water guideline of 100 μg/L (Health and Welfare Canada, 1996). The second community had drinking water that contained less than 1 μgU/L. The indicators of kidney function measured included glucose, creatinine, protein, and β2-microglobulin (BMG). The markers for cell toxicity were alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and *N*-acetyl-β-D-glucosaminidase (NAG). These appear in the urine as a result of cell toxicity (Zamora, et al., 1998). Urinary glucose was found to be significantly different and positively correlated with uranium intake for males, females and pooled data. Increases in ALP and BMG were also observed to be correlated with uranium intake for pooled data. In contrast, the indicators for glomerular injury, creatinine and protein, were not significantly different in the two groups or correlated with uranium intake. The authors conclude that chronic uranium intakes of 0.004 μg/kg-day to 9 μg/kg-day via drinking water affect kidney function and that the proximal tubule is the site of action. The authors note that these effects may represent a manifestation of subclinical toxicity which may not necessarily lead to kidney failure or overt illness. It may, however be the first step in a process where chronic intake of elevated levels of uranium may lead to progressive or irreversible renal injury.

In a later study, Health Canada (1998) investigated kidney effects of exposure to uranium in people living in Kitigan Zibi, a town in Quebec. This town is supplied with drinking water from wells that have uranium concentrations ranging from 10 to 1,418 ppb. Exposure to uranium was estimated by measuring uranium excretion in the urine. Effects on kidney function were determined (as in the previous study) by analyzing urine samples for a variety of parameters and enzymes, including urine volume, urine specific gravity, γ-glutamyl transferase (GGT) and β2-microglobulin (BMG). In this study it was found that for the pooled male and female data there was a statistically significant positive correlation ($p<0.01$) between four parameters associated with tubule effects and uranium excretion (see Table 2, below). These four parameters were urine volume, specific gravity, GGT and BMG. Other parameters related to tubule effects (urinary glucose, ALP, LDH, and NAG) did not show a statistically significant correlation with uranium excretion. Two parameters related to glomerular effects (urinary creatinine and protein) were not correlated with uranium excretion in a statistically significant manner. The data from this study are discussed further in the Dose-Response section below.

Carcinogenicity

A mortality study was conducted on 2,731 males employed at a uranium refining and processing facility. Exposure and smoking habits were not analyzed. No deaths occurred from cancers of the bone or thyroid, but deaths from cancer of the esophagus showed a statistically significant increase (Dupree, 1980).

In uranium miners an increased mortality from lung cancer has been recognized for many years (Pochin, 1985). Lung cancer has been related to the radiation dose to lung tissues. The dose to the lung in uranium mines comes essentially from the radioactive decay products of the radioactive gas radon, rather than from uranium itself. The atmosphere in mines is likely to contain materials such as arsenic and diesel fume polycyclic aromatic hydrocarbons, which have significant carcinogenic effects. These would have confounding effects on any study of the carcinogenicity of uranium itself.

Table 2. Uranium Excretion Correlation Coefficients for Volume Adjusted Data

Biomarkers	Kidney Site Affected	Volume Adjusted Data (pooled male and female)
Urine volume	Tubule	0.50 (0.0001)*
Specific gravity	Tubule	0.35 (0.0088)*
Glucose	Tubule	0.14 (0.31)
Creatinine	Glomerulus	0.24 (0.08)
Protein	Glomerulus	0.23 (0.09)
ALP	Tubule	0.15 (0.29)
LDH	Tubule	0.16 (0.26)
GGT	Tubule	0.37 (0.0064)*
NAG	Tubule	0.15 (0.29)
BMG	Tubule	0.49 (0.0047)*

Legend: * indicates statistically significant at 0.01 level. ALP=alkaline phosphatase, LDH=lactate dehydrogenase, GGT=gamma glutamyl transferase, NAG=N-acetyl glucosamine, BMG=beta microglobulin. Based on Table 7 of Health Canada, 1998.

The cigarette smoking habits of the miners also need to be determined and accounted for in the epidemiological risk assessment. It should be noted that other types of underground mining including iron, lead and fluorspar have also been associated with radon gas-induced lung cancer (Zeise et al., 1987). Therefore, at the present time inhalation of natural uranium has not been demonstrated to be carcinogenic for humans.

Polednak and Frome (1981) described mortality in a cohort of 18,869 white males who were employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge. Standardized mortality ratios (SMRs) for various sites, including lung cancer, bone cancer, leukemia and disease of the respiratory and genitourinary system did not tend to be higher in workers exposed to the highest average levels of uranium dust. Workers in the "alpha chemical department" were exposed to the highest levels of airborne uranium dust. There were no deaths from bone cancer or leukemia, or from chronic nephritis. SMRs for lung cancer were analyzed by age at hire and job classification. The SMR for lung cancer in these alpha chemistry workers hired at $\geq$ 45 years of age was high, based on small numbers. None of the seven lung cancer decedents worked for one year or longer in alpha chemistry.

There are no reports of experimental induction of bone cancer by ingested, injected or inhaled natural uranium in soluble form (Wrenn et al., 1985). However, bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of high specific activity uranium isotopes, ^{232}U and ^{233}U (Finkel, 1953). Lung cancer was produced in rats and dogs, but not in monkeys following continuous inhalation of large amounts of highly soluble UO_2 for two to five years (Leach et al., 1970; Leach et al., 1973).

Wilkinson (1986) has reported that several counties in northern New Mexico displayed high rates of mortality from gastric cancer. Significant differences in sex-specific, age-adjusted, average annual stomach cancer mortality rates during 1970 to 1979 were found between counties with significant deposits of uranium compared to those without significant deposits (Wilkinson, 1986). The identification of uranium deposits is based on a qualitative survey designed to identify areas containing uranium deposits that might be of commercial value. Wilkinson (1986) advanced a working hypothesis that residents of counties with significant deposits of uranium are exposed to higher levels of radionuclides such as radon and radon daughters than residents of counties lacking the uranium deposits.

Genotoxic and Cytotoxic Effects

Uranium miners have been found to have increased frequency of chromosomal aberrations in human lymphocytes, but these have been thought to be due to radon or its radioisotope daughters (Brandom et al., 1978; ATSDR, 1997). Other genotoxic effects have not been adequately tested (ATSDR, 1997).

Blood lymphocyte cultures from two groups of workers exposed to uranium were examined for asymmetric chromosomal aberrations and sister-chromatid exchanges (SCEs). Significant increases were seen in both of these cytogenetic endpoints (Martin, et al., 1991). These investigators interpreted their results as evidence of clastogenic effects of uranium.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The recently published studies of Gilman et al. (1998a-c) provide a basis for a dose response assessment of noncarcinogenic effects caused by chronic uranium intake via drinking water. In particular the 91-day study in Sprague-Dawley rats identifying a subchronic oral LOAEL of 0.06 mg/kg-d for renal and liver lesions in males appears to be a reliable basis. The histological changes that were observed at this lowest dose did not generally increase in number at the higher doses, so these data cannot be said to exhibit a dose-response relationship above the lowest dose tested. This observation diminishes the value of these data as an indication of the beginning of potentially pathological changes.

A similar subchronic LOAEL of 0.05 mg/kg-d was observed in male New Zealand White rabbits although the study was compromised by a microbial infection in four animals. The findings of effects on human kidney function resulting from quite low exposure levels of uranium in drinking water (0.004 μg/kg-d to 9 μg/kg-d) tends to support the animal data and suggests a very broad dose response range, although the effects noted cannot be considered toxic as such (Zamora et al., 1998). One could question the toxic significance of the histological lesions seen in the Gilman et al. studies and while it is often difficult to identify clearly adverse effects in such studies, for the purpose of determining a PHG, OEHHA considers such effects to be adverse albeit weak. Each human kidney contains about one million nephrons, and considerable loss of these is required to reduce kidney function or result in kidney disease. However, chronic subclinical kidney toxicity ought to be considered as a continuum where certain levels of injury may compromise the body's resistance to other environmental insults.

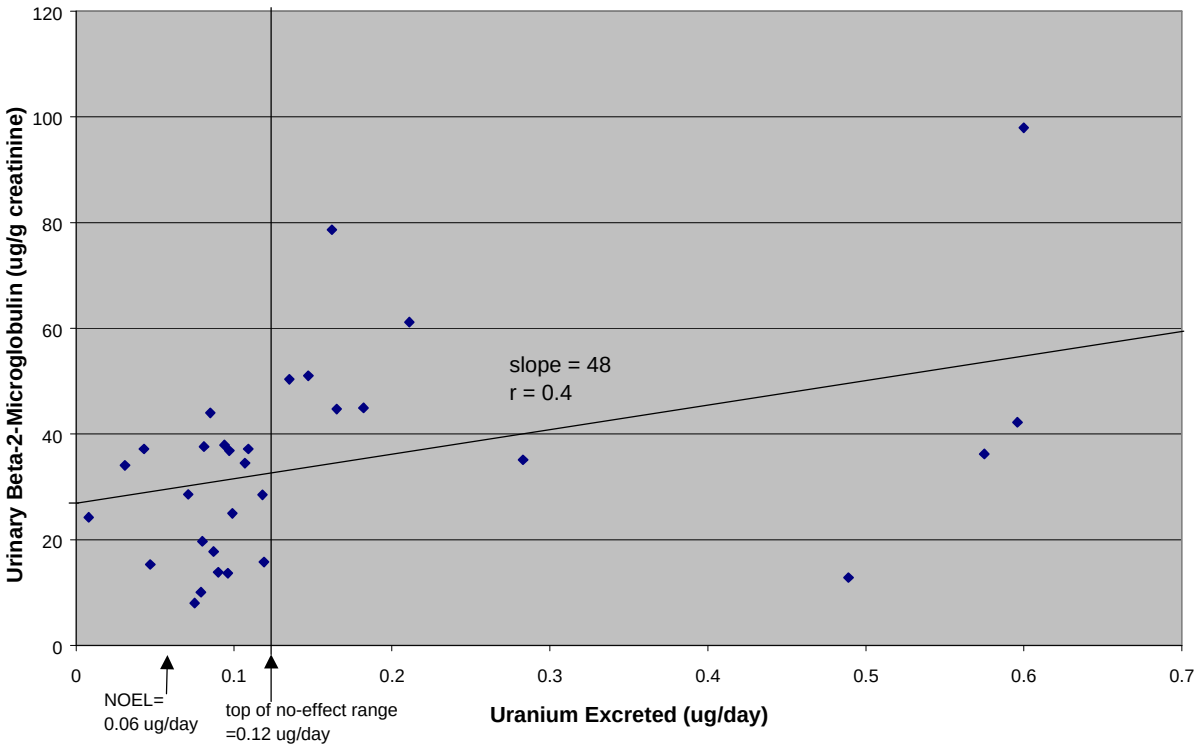
The Zamora et al. (1998) kidney function study compared two communities in Canada based on high and low uranium intake in drinking water. The authors reported that daily uranium intake in the high exposure group was associated with higher urinary glucose levels in males and females. They also reported a positive correlation between individual total uranium intake and individual urinary glucose levels for the high exposure group. Increases in ALP and BMG were also observed to be correlated with uranium intake for the pooled (male and female) data. The range of daily intake associated with increased urinary glucose was from 0.004 to 9 μg/kg. The median high exposure intake in this study was 58 μg/day. Thus, the daily intake was on the order of 1 μg/kg at the median dose level.

As discussed above (page 11) the Health Canada (1998) study found four parameters related to tubule effects to be positively correlated in a statistically significant manner with uranium excretion. These four parameters are urine volume, urine specific gravity, GGT, and BMG. Of these the first two are of questionable specificity, i.e. they may or may not be related to effects of uranium on the kidney tubules. GGT and BMG are more reliable indicators of kidney tubule effects of uranium exposure. Both of these data sets were analyzed by OEHHA using linear regression statistics. Both data sets showed a high degree of correlation (r=0.4 for both data sets). The BMG and GGT data sets were chosen to use for determination of an NOEL for kidney tubule effects caused by uranium in drinking water.

The BMG data set (Figure 1) exhibits a positive correlation between urinary BMG and uranium excreted ($r = 0.40$, $p = 0.0026$). At urinary excretion levels below 0.12 μg/day there is no correlation ($r = 0.010$, $p = 0.97$) even though there are enough data points below this level (n=20)

to show a correlation if there had been one. This shows that exposures below those corresponding to excretion of 0.12 µg/day have no effect on urinary BMG levels, i.e. the variation in BMG levels below this level are essentially random. Since the data between 0 and 0.12 µg/day exhibit no effect, 0.06 µg/day (the midpoint of this range) can be considered an excretion level that corresponds to a NOEL for this endpoint. An effect on BMG begins to be observed at excretion levels of 0.14 µg/day and increases with increasing excretion levels. The GGT data set was analyzed, with similar results. For the GGT data set there was no correlation below the 0.12 µg/day excretion level (r=0.066, p=0.70) but a strong correlation for the whole data set (r=0.41, p=0.002). The 0.06 µg/day excretion level, appears to be a NOEL for both data sets.

Figure 1: Correlation of Urinary BMG with Uranium Excretion (Health Canada, 1998)



The 1998 Health Canada study in Kitigan Zibi is better for risk assessment purposes than the Zamora et al. (1998) study, primarily because the former is based on uranium excretion, which is a more direct measure of uranium reaching the kidney than estimating the exposure based on uranium levels in the drinking water and assumptions about water consumption.

Carcinogenic Effects

U.S. EPA has classified natural uranium as a Group A carcinogen ("human carcinogen based on sufficient evidence from epidemiological studies") because it is an emitter of ionizing radiation. U.S. EPA classifies all emitters of ionizing radiation as Group A carcinogens. U.S. EPA acknowledges that "studies using natural uranium do not provide direct evidence of carcinogenic potential." However, studies with radium and certain isotopes of uranium provide evidence for the carcinogenicity of ionizing radiation in humans (U.S. EPA, 1991a, b). U.S. EPA also considers agents emitting ionizing radiation to be mutagens and teratogens.

Mays et al. (1985) estimated the lifetime cancer risk of daily intake of uranium in drinking water based on data from induction of skeletal cancers by radium isotopes. They estimated that exposure of one million persons to 5.0 pCi per day from uranium isotopes in drinking water would be expected to result in 1.5 additional bone sarcomas. This is equivalent to a cancer risk for uranium in drinking water of 6.0×10^{-7} per pCi/L (assuming consumption of two liters of water per day). This is virtually identical to the U.S. EPA's 1991 estimate.

More recently U.S. EPA has developed carcinogenic potencies or risk coefficients for over 100 radionuclides including six isotopes of uranium (U.S. EPA, 1994, 1999). The risk coefficients developed apply to an average member of the public in that estimates of risk are averaged over the age and gender distributions of a hypothetical closed population with an unchanging gender ratio whose survival functions and cancer mortality rates are based on the 1989-1991 U.S. decennial life table (NCHS, 1997) and U.S. cancer mortality data for the same period (NCHS,1992, 1993a, 1993b). For each radionuclide and exposure route both mortality and morbidity risk coefficients are provided. The five steps involved in computing the risk coefficients for internal exposure are as follows:

- Step 1 (Lifetime risk per unit absorbed dose at each age): For each of 14 cancer sites radiation risk models are used to calculate gender-specific lifetime risks per unit of absorbed dose.
- Step 2 (Absorbed dose rates as a function of time post acute intake at each age): Age-specific biokinetic models are used to calculate the time-dependent inventories of activity in various regions of the body following an acute intake of a unit of activity of the radionuclide. Six ages are used: 100 days, and 1, 5, 10, 15, 20-25 years.
- Step 3 (Lifetime cancer risk per unit intake at each age): For each cancer site, the gender-specific values of lifetime risk per unit absorbed dose received at each age (from the first step) are used to convert the calculated absorbed dose rates to lifetime cancer risks, for the case of acute intake of one unit of activity at each age x_i.
- Step 4 (Lifetime cancer risk for chronic intake): It is assumed that the concentration of the radionuclide in the environmental medium remains constant and that all persons in the population are exposed throughout their lifetimes.
- Step 5 (Average lifetime cancer risk per unit activity intake): Because a risk coefficient is an expression of the radiogenic cancer risk *per unit activity intake*, the calculated lifetime cancer risk from chronic intake of the environmental medium must be divided by the expected lifetime intake. For a more thorough explanation of these five steps see U.S. EPA, 1999.

Analyses involving the risk coefficients should be limited to estimation of prospective risks in large existing populations, rather than being applied to specific individuals. Also the risk coefficients may not be suitable for assessing the risk to an average individual in an *age-specific* cohort. All computations of dose and risk were performed using DCAL, a comprehensive biokinetics-dose-risk computational system designed for radiation dosimetry (EPA, 1999). DCAL has been extensively tested and has been compared with several widely used solvers for biokinetic models and systems of differential equations. DCAL was used by a task group of the ICRP to derive or check the dose coefficients given in its series of documents on age-specific doses to members of the public from the intake of radionuclides (e.g., ICRP, 1996).

The two most common uranium isotopes in drinking water are ^{234}U and ^{238}U with lifetime mortality risk coefficients for exposure via tap water of $1.24\times10^{-9}Bq^{-1}$ and $1.13\times10^{-9}Bq^{-1}$, respectively. Multiplying by 0.037 Bq/pCi converts these coefficients to lifetime risks of 4.6×10^{-11} and 4.2×10^{-11} per pCi. Since the isotopic ratio of $^{234}U/^{238}U$ in California groundwater is 1.32 ± 0.3 (Wong et al., 1999) the combined risk coefficient for uranium in California water is $4.4\times10^{-11}(pCi)^{-1}$. Assuming a lifetime to be 25,550 days (70 years) and daily water consumption to be 2L, a unit risk of $2.3\times10^{-6}(pCi/L)^{-1}$ can be calculated. The U.S. EPA risk coefficient incorporates a gastrointestinal uptake factor (F1) of 0.02 (2 percent).

CALCULATION OF PHG

Noncarcinogenic Effects

We will calculate public-health protective concentrations (C) for noncarcinogenic endpoints, using first the rat studies of Gilman et al. (1998a), then using the human data from Health Canada (1998).

Calculations Based on Data from Rat Studies

First, using the data from Gilman et al. (1998a), a public health-protective concentration (C) for uranium in drinking water (in mg/L) can be calculated following the general equation for noncarcinogenic endpoints:

$$C = \frac{\text{NOAEL or LOAEL x BW x RSC}}{\text{UF x W}}$$

where,

NOAEL or LOAEL = No-observed-adverse-effect-level or Lowest Observed Adverse Effect Level (LOAEL of 0.06 mg/kg-d for toxicity in rats evidenced by a variety of kidney and liver histological lesions from Gilman et al., 1998a).

BW = Body weight default for an adult human (70 kg)

W = Daily water consumption default for an adult (2 L/day)

RSC = Relative source contribution of 40 percent (0.4)

UF = Uncertainty factor of 300:This includes a factor of 3 for LOAEL to NOAEL assuming the histological lesions in the rat study are relatively mild adverse effects; a factor of 10 for interindividual differences in sensitivity to uranium toxicity; 1 for interspecies differences since the responses in humans and experimental animals appear very similar; and 10 for extrapolation from a 91 day study to lifetime exposure.

Therefore,

$$C = \frac{0.06 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.4}{300 \times 2 \text{ L/day}} = 0.0028 \text{ mg/L} = 0.003 \text{ mg/L} = 3 \text{ ppb (rounded)}$$

The C value of 0.003 mg/L is equivalent to approximately 2.4 pCi/L (based on a specific activity of 0.79 pCi/μg).

Repeating the same calculation for a child:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W}$$

where,

LOAEL = Same as for the adult calculation

BW = An assumed default child's body weight (10 kg)

W = Daily water consumption for a child (1 L/day)

RSC = Relative source contribution of 40 percent (0.4 as for the adult)

UF = Uncertainty factor of 300 (as for the adult).

Therefore,

$$C = \frac{0.06 \text{mg/kg-day} \times 10 \text{ kg} \times 0.4}{300 \times 1 \text{ L/day}}$$

$$= 0.0008 \text{ mg/L} = 0.8 \text{ ppb.}$$

The health-protective concentration based on noncarcinogenic effects in children is 0.0008 mg/L, equivalent to 0.63 pCi/L. This calculation is based on rat data that exhibited an apparent LOAEL, but did not exhibit a positive dose-response relationship at doses above the LOAEL.

Calculations Based on Data from Human Studies

The human data from Health Canada (1998) can be used to calculate a health conservative value as follows. The excretion NOEL of 0.06 μg/day from the Health Canada (1998) human study can be used to calculate a C value for natural uranium in drinking water. If we assume that the individuals are in equilibrium, the uranium excreted would equal the uranium intake multiplied

by the percentage absorbed. In its review of the literature, U.S. EPA found values for gastrointestinal absorption of uranium in humans ranging from 1 to 30 percent (U.S. EPA, 1991a, b). As discussed above in the section on absorption (page 3) the value for absorption recommended by the U.S. EPA in Federal Guidance 13 (U.S. EPA, 1999) is 2 percent. Assuming 2 percent absorption the NOEL would be 50 times the excretion NOEL of 0.06 μg/day or 3.0 μg/day. This NOEL is expressed in μg/day, so body weight is not included in the equation.

$$C = \frac{NOEL}{UF \times 2L/day}$$

No RSC is included in the equation because the data are taken from an ecological human study that directly compares drinking water exposures. Since this is a NOEL based on human data, the only uncertainty factor needed is a factor of 10 for intra-human variability, i.e. to protect sensitive individuals including 1.) children, and 2.) individuals with subclinical kidney impairment. At these low levels, only lifetime or very long exposures would be effective, so we can base the calculation on adult water consumption (2 L/day). The equation thus becomes:

$$C = \frac{3\ \mu g/day}{10 \times 2\ L/day} = 0.15\ \mu g/L \text{ or } 0.2 \text{ ppb.}$$

This number is lower than the 0.8 ppb calculated above on animal data. Because it involves less uncertainty (no interspecies extrapolation or long-term exposure extrapolation), is specifically protective of the effects of concern in humans, and because the animal data did not show a clear dose-response, the 0.2 ppb based on human data is the preferable number to use for a health protective concentration based on noncarcinogenic effects to the kidney.

Carcinogenic Effects.

As noted above under Dose/Response Assessment the unit risk of uranium in California drinking water is 2.12×10^{-6} $(pCi/L)^{-1}$. Therefore the drinking water concentration corresponding to negligible risk is given by:

Drinking water concentration = Risk ÷ Unit Risk

Negligible risk concentration = $10^{-6} \div 2.3 \times 10^{-6}$ $(pCi/L)^{-1}$ = 0.43 pCi/L.

This calculation and those above for noncarcinogenic health effects are based on point estimates rather than distributions. Probabilistic or stochastic methods can be used to calculate a distribution of safe drinking water levels, thereby making use of the information available concerning distributions, and reducing the uncertainty associated with the use of single point values. An alternate expression for health protective concentrations with distributions represented by bold face symbols is as follows:

$$C = (R/RC) \times (1/L) \times (0.02/\mathbf{F1}) \times (1/\mathbf{W}) = pCi/L$$

where,

R	=	Negligible lifetime individual risk of 10^{-6}
RC	=	Risk Coefficient of 4.20×10^{-11} $(pCi)^{-1}$lifetime
L	=	Lifetime of 74 yr or 27,000 d/lifetime (rounded)
F1	=	Intestinal absorption fraction lognormal distribution (Wrenn et al.,1985)
W	=	Daily water intake in L/d lognormal distributions (Ershow & Cantor,1989)

A variant of this relation employed separate distributions for body weight (BW) in kg and specific water intake (WI) in L/kg-d with an assumed correlation of 0.5 (data not shown). However, the simpler expression is preferred. The RC value was determined for F1 = 0.02 and the F1 distribution adjusts this value based on the data of Wrenn et al.(1985). The distribution parameters used in the analyses are shown in Table 3. The distributions are empirical but similar to modeled distributions over the range of predicted distribution values i.e., 10-90 percent (OEHHA, 1996).

Table 3. Parameters Used in Stochastic Calculations of Health Protective Concentrations of Uranium in Drinking Water

Variate	Distribution	Parameters Mean ± SD	Limits	Reference
BW	Lognormal	71.0 ± 15.9 kg	45.0,115.0 kg	Finley et al., 1994
W (total)[1]	Lognormal	2.206 ± 0.886 L/d	1.0, 7.0 L/d	Ershow & Cantor, 1989
W (tap)[1]	Lognormal	1.263 ± 0.674 L/d	0.5, 3.5 L/d	Ershow & Cantor, 1989
F1	Lognormal	0.0186 ± 0.0216	0.003, 0.078	Wrenn et al., 1985
Specific activity	Normal	0.79 ± 0.10 pCi/µg	0.45, 1.20 pCi/µg	Wong et al., 1999

Note: (1) Western U.S. Regional data all individuals. Tap water includes water used for drinking, making beverages etc. total water includes water used in food preparation, consumed in bottled drinks etc..

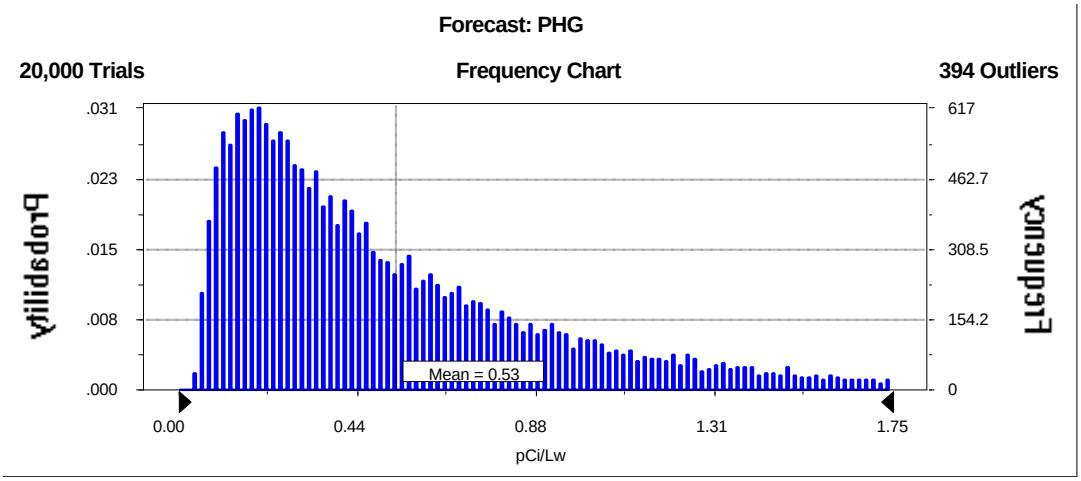
Simulations were performed with Microsoft Excel v. 4.0 and Crystal Ball v. 4.0 (Decisioneering, Inc.) software employing 20,000 trials and latin hypercube sampling. Selected percentiles of the predicted distributions of safe drinking water concentrations with negligible lifetime extra cancer risk from uranium's ionizing radiation are shown in Table 4. As can be seen safe values for total water intake for all individuals range from 0.13 to 1.12 with a mean of 0.53 pCi/L (see also Figure 2). For consumers of tap water only, the values are about double those for total water, or about 0.2 to 2.25 with a mean of 1.0 pCi/L.

Table 4. Distributions of Health Protective Concentrations for Natural Uranium in California Drinking Water (pCi/L)*

Target Population, Water Exposure	10%	50%	Mean	90%
Western Regional Population, Total Water Exposure	0.13	0.40	0.53	1.12
Western Regional Population, Tap Water Exposure	0.22	0.74	1.04	2.26

*Note: Concentrations equivalent to 1×10^{-6} theoretical lifetime extra risk of cancer mortality

Figure 2. Distribution of Safe Drinking Water Concentrations of Natural Uranium based on distribution of total water intake from Ershow and Canter, 1989.



Based on considerations of theoretical radiation risk and exposure via drinking water, a health protective concentration for natural uranium in drinking water would be 0.44 pCi/L from the deterministic calculation and 0.53 pCi/L from the mean distribution value for total water intake

from the stochastic analysis. According to either analysis, a *de minimis* cancer risk level for the ionizing radiation effects of natural uranium in drinking water is approximately 0.5 pCi/L.

Based on consideration of the noncarcinogenic nephrotoxic effects, a health protective concentration would be 0.2 μg/L. Based on the California specific activity of 0.79 pCi/μg, 0.2 μg/L corresponds to 0.16 pCi/L, which can be rounded to 0.2 pCi/L. This value is lower than the 0.5 pCi/L de minimis cancer risk level. The cancer risk at 0.2 pCi/L would be given by the following calculation.

Cancer risk at proposed PHG = 0.2 pCi/L $\times$ 2.3×10^{-6}(pCi/L)$^{-1}$= 5×10^{-7}

A level of 0.2 pCi/L would therefore be protective for both kidney toxicity and cancer. The proposed PHG for natural uranium in California drinking water is 0.2 μg/L (0.2 pCi/L).

RISK CHARACTERIZATION

The proposed PHG of 0.2 ppb (0.2 pCi/L) for natural uranium in drinking water is based on a study of a human population (Health Canada, 1998) that examined measures of kidney function, urinary β2-microglobulin (BMG) and γ-glutamyl transferase (GGT), related to kidney tubule effects. One of the sources of uncertainty in this calculation has to do with whether this effect is truly an indicator of the beginning of an adverse effect, or whether it is just a transient effect not related to adverse kidney effects. By using this endpoint as the basis of a PHG calculation, we are regarding it as an indicator of an incipient change in kidney function that can lead ultimately to frankly adverse effects such as breakdown of tubular function. The BMG and GGT data are supported by the data for two other parameters (urine volume and specific gravity) related to tubule effects in the same study that also showed a positive correlation with uranium excretion. Effects on tubule function were observed in an earlier human study (Zamora et al., 1998) and histological effects were noted in animal studies (Gilman et al., 1998 a-c). However, the kidney effects observed in the studies by Gilman et al. did not show a positive dose response relationship throughout the range of doses studied.

Another source of uncertainty is intrahuman variability in susceptibility to kidney effects. Individuals with compromised kidney function will of course be more sensitive to the nephrotoxic effects of uranium. OEHHA has used the standard default of 10 to account for this variability.

In interpreting the Health Canada (1998) human study for risk assessment, OEHHA has assumed that the individuals with low drinking water exposures (below 0.12 μg/L) received the same exposure to uranium from food and other non-water sources as the individuals who were exposed to higher levels of uranium in their drinking water. There were no individuals in the study who received zero exposure to uranium. This is the basis for not using a relative source contribution (RSC) in the calculation. This assumption is needed because there are no data on exposures to these individuals from other sources. In the absence of data an assumption of equal exposure from these other sources appears to be the simplest and most likely assumption.

The 10^{-6} cancer risk level of 0.5 pCi/L has been calculated based on the carcinogenic effects of ionizing radiation. This level would correspond to a *de minimis* risk level for the carcinogenic effects of ionizing radiation from natural uranium in drinking water. A number of assumptions were made in calculating this *de minimis* risk level. Each of these assumptions is a source of uncertainty. It was assumed that ionizing radiation (particularly alpha particles) emitted by natural uranium would be as carcinogenic as ionizing radiation emitted by more highly

radioactive substances including man-made isotopes of uranium. This assumption and extrapolation is the source of some uncertainty. There are a number of studies indicating that the radiogenic dose response may be nonlinear or linear-quadratic or that tumors develop more slowly at low doses (e.g., Raabe et al.,1980; Billen, 1990; Makinodan and James, 1990; Cohen, 1995, and Pollycove, 1998). U.S. EPA has characterized such effects in terms of a dose and dose rate effectiveness factor (DDREF): e.g., a DDREF of three means the risk per unit dose observed at high acute doses should be divided by three before being applied to low dose (dose rate) conditions (U.S. EPA, 1999). With the possible exception of lung cancer, current scientific data generally indicate DDREFs between 1 and 3 for human cancer induction. For uranium and radionuclides emitting high-LET alpha radiation, the radiobiological results generally support a linear nonthreshold dose response, except for a possible fall-off in effectiveness at high doses (U.S. EPA, 1999). At this point it appears that the linear paradigm of radiogenic risk dose response best satisfies the requirements of the PHG mandate with respect to waterborne natural uranium at low levels. It must be emphasized that implied risk estimates for consumption of uranium in drinking water are *theoretical risks*. It is noteworthy that Mays et al. (1985) arrived at a similar estimate of the cancer potency of uranium, based on a different methodology.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using UFs, body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20 to 80 percent with the default of 20 percent being used when other sources of exposure are recognized (e.g., food, air) and 80 percent when the exposure is thought to be mainly from drinking water.

U.S. EPA uses the following procedure in promulgating MCLGs:

1. Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate. If a RSC of 0.5 was included the calculated uranium concentrations would be lower by a factor of two.

Gastrointestinal absorption of uranium for humans was assumed to be 2.0 percent. The range of values identified in the literature is 1 to 30 percent (U.S. EPA, 1991a, b). Actual gastrointestinal absorption may vary from individual to individual. In the stochastic analysis described above OEHHA used the range of values from Wrenn et al. (1985) assuming a lognormal distribution, specifically 1.86 ± 2.16 percent (range 0.3 to 7.8 percent).

Standard default assumptions of 70 kg body weight for adults, and two liters per day drinking water consumption were made. Actual body weights and drinking water consumption vary over a wide range. In the stochastic analysis above we incorporated a number of water consumption distributions from U.S. national and western regional data sets published by Ershow and Cantor (1989). The range of predicted safe concentrations (pCi/L) was approximately an order of magnitude from the 10^{th} to the 90^{th} percentiles. The proposed PHG is between the median and mean of the predicted distribution based on total water consumption. It should be noted that the stochastic analysis employed exposure variates only since OEHHA currently has no proposed methodology for addressing the uncertainty in dose response mentioned above.

Ionizing radiation has been conclusively shown to be carcinogenic in humans, therefore U.S. EPA classifies all emitters of ionizing radiation as Class A carcinogens. U.S. EPA also considers agents emitting ionizing radiation to be mutagens and teratogens. There can be little doubt that high levels of natural uranium in drinking water would present cancer and other risks to humans who consume such water over a long period of time. In order to provide a reference for protection against the theoretical cancer risk at lower concentrations, a *de minimis* risk level has been calculated and presented based on the ionizing radiation emitted by natural uranium.

OTHER STANDARDS AND REGULATORY LEVELS

U.S. EPA has proposed an MCLG of 0 pCi/L for uranium, based on their classification of it in Carcinogen Group A (FR 56, 33050, July 18, 1991). U.S. EPA also reported an adjusted acceptable daily intake (AADI) of 60 μg/L, or 40 pCi/L.

U.S. EPA has also proposed an MCL of 20 μg/L (equivalent to approximately 30 pCi/L, based on a specific activity of 1.3 pCi/μg (Fed. Reg. 56: 33050, July 18, 1991). This proposed MCL corresponds to a cancer risk of $1x10^{-5}$, as estimated by U.S. EPA. Economic and technical feasibility were considered in arriving at this proposed MCL. This proposed MCL has never been made final.

The State of California adopted an MCL of 20 pCi/L for natural uranium based on kidney toxicity to adults (Lam et al., 1994; CDHS, 1987). This State MCL was based on a risk assessment which identified Novikov and Yudina (1970) as the key study. This study has been superseded by the more recent studies (Gilman et al., 1998a-c; Zamora et al, 1998; Health Canada, 1998) upon which the current risk assessment is based. The more recent studies identify kidney effects at lower levels of exposure than those described in the Novikov and Yudina report.

In the latest review by the National Research Council (NRC, 1983), a suggested no-adverse-response-level (SNARL) in drinking water for chronic exposure of 35 μg/L (23 pCi/L) was based on noncarcinogenic responses to adults. The National Workshop on Radioactivity in Drinking Water recommended that the limiting concentration for natural uranium in drinking water should be 100 μg/L (67 pCi/L) (Wrenn et al., 1985).

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